Global epidemiology of influenza A and B

Caini, S.

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Chapter 1

General Introduction

The primary objectives of influenza surveillance are to issue early warnings that enable health systems, governments and supranational organizations (such as the European Centre for Disease Prevention and Control [ECDC] or the World Health Organization [WHO]) to respond to influenza epidemics in the most timely and appropriate manner; and to perform a continuous monitoring of circulating viruses, in order to promptly detect novel and/or highly virulent strains and update the vaccine composition accordingly [1]. To achieve this dual objective, it is of paramount importance that both the epidemiological and virological sides of influenza surveillance are in place and tightly linked with each other, as both provide essential information and complement each other.

The global capacity for influenza surveillance has been strengthened and extended to an increasing number of countries and territories in recent years, in particular since the run-up of the A(H1N1) 2009 pandemic [2]. This greatly enhanced surveillance activity has produced a growing mass of epidemiological and virological data, unprecedented in terms of quantity, quality and geographic coverage. The exploitation for research purposes of this data has great potential, for several reasons. On the one side, the careful and extensive evaluation of the output of a process (here, influenza surveillance) can contribute to increase its efficacy and help make a more rational use of resources, which is critical in both high- and low-resources countries. In addition, a better understanding of influenza epidemiology (in terms of timing of epidemics, patterns of transmission and spread, burden of disease, etc.) is highly needed to help policy-makers implement and refine public health interventions that are based on robust scientific evidence.

In accordance with this premise, in this thesis we will exploit existing influenza surveillance data in order to explore different aspects of global influenza epidemiology. The overall aim of this thesis is to produce knowledge that may help optimize the strategies of prevention and control of influenza where they are already in place, and support their implementation in countries where they are still lacking or inadequate. The main research questions are the study of the main epidemiological characteristics of influenza B (and how these compare with influenza A and its subtypes); the description of spatio-temporal patterns of seasonal influenza A and B epidemics in different world regions; and the study of the link between the results of the above investigations and the strategies for influenza prevention and control.

1.1 How to contain influenza epidemics?

1.1.1 A historical perspective

The twentieth century has seen an unprecedented epidemiological transition in developed countries [3]. Some of the most fatal human infectious diseases (like plague, cholera and syphilis), which were highly incident until a few centuries (or even few decades) ago, have been reduced to negligible incidence and mortality rates in most developed countries. Smallpox was eradicated, and other infectious diseases (such as polio, measles and hepatitis B) might follow the same fate in the near future. The discovery and synthesis of drugs with antibiotic activity further contributed to reduce the case-fatality ratio of infectious diseases whose incidence and mortality had already greatly declined, like tuberculosis. In some other cases, however, the progresses have not been as successful. Some infectious diseases, like malaria or dengue, persist as major health threats mainly in developing countries in the tropics and subtropics. In contrast, influenza stands out as one of the very few infectious diseases whose burden (of disease) is estimated to be very high at all latitudes [4-6].

Influenza has accompanied humankind throughout its history, and epidemics possibly caused by influenza viruses can be traced back to ancient documents like early Greek writings and medieval reports [7]. The first well documented pandemic was the so-called "Russian" pandemic in 1889 [8]. Coming in three waves during 1918-1919 (spring 1918, autumn 1918, and winter 1919), the notorious "Spanish" pandemic outnumbered the sum of combatants and civilians who died as a result of the First World War. In fact, the 1918-1919 pandemic caused an estimated 2.64 million excess deaths in Europe, i.e. more than 1% of the entire European population of the time [9], and approximately 50 million deaths worldwide [10]. Influenza and influenza-associated pneumonia were the first cause of death in the USA already back in 1900 [11], and have been responsible for the largest number of infectious disease deaths throughout the twentieth century in the USA [12].

Likewise most infectious diseases, influenza-like illness incidence and influenza mortality have been declining markedly over the course of twentieth century in most developed countries [12-13]. A large share of the decline in influenza mortality was initially made possible by the huge improvements in sanitation, nutrition, and living and working conditions of the general population. Later on, this process was pushed forward by discoveries and innovations in medicine and public health. These include the synthesis and growing availability of antibiotics effective for the treatment of influenza-associated pneumonia; the “invention” of modern infectious diseases surveillance system [14]; and the improvements in diagnostic techniques made possible by the advance in immunology. An important milestone was the isolation of influenza viruses in 1933: this led to the development of monovalent A vaccines within a few years, which were then improved to include a B strain (the first bivalent vaccine dates back to 1942), two A strains (first trivalent vaccine in 1978) and two B lineages (in 2013) [15]. Despite these major conquests, the last sixty years have witnessed the occurrence of three pandemics (in 1957, 1968 and 2009), and influenza and its sequelae continue to represent a challenge for governments and health professionals throughout the world.

1.1.2 Management of influenza epidemics: a unique challenge

Influenza differs from most other infectious diseases in terms of the degree to which it can be prevented or controlled by the traditional means of combating human infectious diseases. The causes of this lie in a number of features of influenza viruses mainly related to their biology, ecology and evolutionary dynamics. First, the effectiveness of influenza vaccines is still not satisfactory [16-17], because of the frequent co-circulation of multiple virus strains, the evolving nature of influenza A viruses (via antigenic drift and shift), the difficulty to predict what strains will dominate the next season, the moderate protection provided against mismatched strains [18], and the rapid decline of vaccine-induced protection over time [19]. Second, type A influenza viruses have a vast animal reservoir, and the large populations of some host species (e.g. those raised by man, like pigs and poultry) serve as a “mixing pot” that favours the emergence of new strains and their transmission to humans. Third, the very high transmissibility of influenza viruses and the growth in international trades and travel mean that the containment of epidemics (e.g. by quarantine or isolation) is not an easily enforceable preventive measure. Fourth, antiviral drugs may help mitigate the health consequences of outbreaks in institutions like long-term care facilities [20], but their role in containing larger influenza epidemics or pandemics is unclear [21]. These characteristics of influenza viruses and of their interactions with human populations imply that the above mentioned results achieved during the twentieth century against many infectious diseases are not currently accessible for influenza. However, we now know that the impact of influenza epidemics on human populations can be effectively palliated, although this requires a sustained and active involvement of many actors (governments, medical professionals, vaccine producers) and an unceasing coordination at supranational level.

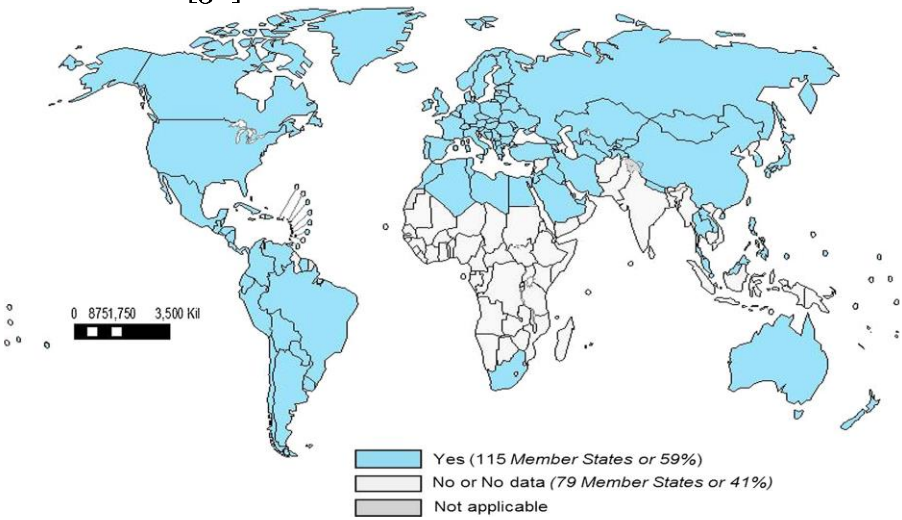
The key elements in todays’ efforts to contain the burden of disease of influenza are vaccines, surveillance, and preparedness. Annual influenza vaccination campaigns help protect vulnerable people (like the elderly population, ill people, and pregnant women) and avert many influenza-associated hospitalizations and deaths. Accurate real-time monitoring of influenza activity allows one to issue early warnings on the start, peak and decline of influenza epidemics, and expedites the detection of emerging virus strains. Influenza pandemic preparedness has established itself as a priority globally, as it is critical in minimising the health and economic impact of future inevitable but unpredictable pandemics. It is important to emphasize that the above activities must necessarily be coordinated and harmonized through all decision-making levels (from single regions and countries up to supranational and global entities) to reach the maximum of their effectiveness. In fact, novel influenza A viruses (both drift variants and new pandemic strains) can emerge virtually anywhere in the world, are transmitted rapidly among humans, and can spread to all continents within a few weeks' time. In this perspective, the advantages of expanding the global surveillance network and coordinating it at supranational level have been long recognized by the scientific community. The Global Influenza Surveillance and Response System (GISRS) (formerly known as Global Influenza Surveillance Network, GISN) was established in 1952 and currently comprises 6 WHO Collaborating Centers and 142 National Influenza Centers (NICs) around the world [22]. Its missions are to conduct influenza virological surveillance globally, issue recommendations on laboratory procedures and vaccines, detect influenza outbreaks, and serve as an alert mechanism for the emergence of new influenza viruses.

1.2 Influenza prevention and surveillance: a global overview

Preventative measures for influenza include the use of antivirals [23] and attempts to reduce its transmission through travel restrictions [24], border entry screening [25], school closures [26], and hygiene behaviours (e.g. hand washing and the use of facemasks) [27], but vaccination is widely accepted as the most effective way to prevent infection and severe outcomes caused by influenza illness [28-29]. Although the burden of influenza is high wherever this has been systematically assessed [30], the efforts that have been and are being made to reduce it through vaccination are, however, heterogeneously distributed in the different world regions.

In developed countries of Europe, North America and Oceania, the life expectancy at birth has increased greatly over the past decades, the median age of the population is now much higher than in the past, and the survival of people living with chronic diseases (like cardiovascular diseases and diabetes) has greatly improved as well. As a result, the share of the population that is at risk of having a poor prognosis when infected with influenza has expanded. In these countries, the annual influenza vaccination campaigns prevent a large proportion of influenza illness, hospitalizations and influenza-related deaths [31]. In contrast, vaccination campaigns are not implemented routinely in many low-income countries (Figure 1.1) [32]. However, most cost-effectiveness studies point out that a commitment in this sense would affect positively the health status and economic development of these countries, and should represent a high-priority strategic investment for local governments and supranational organizations [33-34].

Figure 1.1. World map with WHO member states reporting to have a national seasonal Influenza vaccine programme in 2014. From Ortiz JR et al. 2016 [32].



The picture is more complex and rapidly evolving as regards influenza surveillance in the different world areas. Efficient communicable diseases surveillance systems have been operating for decades in developed countries of Europe, North America and Oceania. Most countries in these world regions have in place both population- and hospital-based influenza surveillance systems, which form a vast and interconnected surveillance network and collect good quality epidemiological and virological data. In contrast, countrywide population-based influenza surveillance systems needed to be strengthened, or even established, in several low-income countries until very recently [35]. As already mentioned, the 2009 influenza pandemic has represented a powerful stimulus for expanding the surveillance network to countries previously devoid of it, and for increasing the availability of high-performance laboratory techniques for the detection and characterization of influenza viruses from biological samples. A thorough analysis of the data produced in the process (which very frequently has been shared with the WHO and made available in public repositories) is urgent and has the dual objective of expanding knowledge on influenza epidemiology and burden of disease, and understanding what are (and where are localized) the knowledge gaps that still need to be filled.

1.3 Knowledge gaps in the epidemiology of influenza

1.3.1 Influenza B

The growing availability of influenza surveillance data allows one to focus on research areas that have been less frequently explored until now. One of the topics on which we will put the most attention in this thesis is influenza B. Up until a few years ago, most research on influenza targeted type A viruses, mainly because of their higher variability and their potential to cause pandemics, while type B influenza has been comparatively neglected, although its burden of disease was thought to be substantial as well [36]. In part, the lack of interest was due to the common belief that the illness caused by influenza B is on average milder, and leads less frequently to complications, hospitalizations and influenza-associated death, than influenza A, but this has been challenged recently by a number of reports [37-39]. The influenza B virus has evolved into two antigenically distinct lineages (B/Victoria and B/Yamagata) since 1970s [40]. Only one lineage is represented in the annual trivalent influenza vaccine (TIV) at any time; however, our ability to predict what influenza B strain will dominate next season is poor, and the frequency of vaccine mismatch has been substantial in recent years [41-42]. The recent licensure of quadrivalent influenza vaccine (QIV) comprising B virus strains belonging to both lineages requires that the epidemiology and burden of disease of influenza B is better understood, in order to make it possible to compare the relative costs and benefits of alternative vaccination strategies. A main goal of this thesis is therefore to better characterize the epidemiology of influenza B, in particular by comparing its metrics with that of influenza A and its subtypes.

1.3.2 Temporal patterns of influenza epidemics, with special focus on tropical countries

Much is known on the spatiotemporal patterns of influenza epidemics in temperate countries of the Northern and Southern hemispheres, while comparatively less research has been performed in tropical countries, where one third of the whole world population lives [43]. Although somewhat unavoidable, it is regrettable that much of the gap in knowledge about influenza epidemiology is precisely in the tropical regions, where most low-income countries are located. However, the recent rise in the availability of influenza surveillance data allows studying the spatio-temporal patterns of influenza epidemics in nearly all world areas, which has important implications for the determination of the optimal timing to vaccinate in different regions. In this thesis, we will give special attention to the study of the epidemiology and spatio-temporal patterns of influenza epidemics in tropical countries and, in particular, Latin America.

1.3.3 Deepening the knowledge on influenza epidemiology in Europe

Influenza epidemiology in Europe has been the subject of extensive research, yet there are some issues that remain to be clarified. The availability of high-quality surveillance data from a growing number of countries makes it possible to conduct very in-depth investigations of how influenza viruses spread across Europe, with a very much enhanced accuracy and geographic detail. Also, influenza time-series are today available for up to twenty consecutive years for several European countries, which allow assessing whether changes have occurred over time in the main characteristics of influenza epidemics in Europe. Ecologic interactions between infectious agents and human populations are dynamic in their essence, and the populations' health needs may therefore evolve over time [44-45]. Therefore, it is critical to monitor on a continuous basis whether changes occur in how humans are affected by influenza, as this may help understand whether what is being done for its prevention is still the best that can be done. This is especially important given the constant pressure towards optimizing any public interventions (by improving their efficacy, efficiency and value-for-money) in a scenario of rising healthcare costs and shortage of economic and human resources. Consistently, in this thesis we will turn our attention also towards the developed countries of the Northern hemisphere (focusing in particular to Europe); give an in-depth description of temporal patterns of spread, geographic diversity, and changes over time of influenza epidemics in these countries; and discuss the implications for the existing influenza prevention and control strategies in this world area.

1.4 Aims and outline of the thesis

As mentioned above, this thesis aims to provide more insight into the global epidemiology and patterns of spatiotemporal spread of influenza A and B epidemics, and to make recommendations for improving influenza prevention and control strategies in different world areas.

In the **chapters 2** and **3** of this thesis, we will present a comprehensive analysis of the epidemiological characteristics of influenza B, in absolute terms and in comparison with influenza A and its subtypes. In **chapter 2**, we aim to determine how frequently influenza B circulates or even dominates the epidemic season, and assess the frequency of influenza B mismatches with the vaccine, in countries of the Southern and Northern hemispheres and of the inter-tropical belt. The objective of **chapter 3** is to assess whether different influenza virus types (A, B) and subtypes (H3N2, pre-pandemic H1N1, 2009 pandemic H1N1) preferentially affect people of different age (children, adolescents, adults and elderly).

The next chapters of the thesis will more closely aim on establishing a link between influenza epidemiology and the policies of influenza prevention and control in different world regions. In **chapter 4**, we will examine the temporal characteristics of influenza epidemics (overall and separately for influenza A and B) in countries of the Northern and the Southern hemispheres and of the inter-tropical belt, and discuss their potential implications for influenza vaccination programs. Determining the optimal time to vaccinate is crucial in order to ensure that influenza vaccination campaigns achieve maximum effectiveness, therefore the results reported in this chapter have important implications for influenza vaccination programs globally. In **chapter 5,** we will more closely focus on the epidemiology of influenza in Latin America. The overall objectives of this chapter are to assess the availability and quality of influenza surveillance data in the region, and carry out a comparison between current vaccination policies and vaccination recommendations based on the analysis of influenza time-series.

In the last two chapters, the spotlight will be on influenza epidemiology in the temperate climate countries of the Northern hemisphere, and in particular on the WHO European region (a large area including over 900 million inhabitants in 54 countries, that stretches from Portugal, Ireland and Iceland in the West to the Russian Federation in the East). In **chapter 6,** we will describe the spatiotemporal patterns of influenza epidemics across the WHO European region (including the study of latitudinal and longitudinal gradients of transmission) and assess the validity of the influenza transmission zones proposed by the WHO using an innovative cluster models approach. Finally, in **chapter 7** we aim to explore whether the timing of the peak of influenza epidemics has changed in countries of the WHO European region during the last two decades (i.e. during 1996-2016).

Chapter 8 will be devoted to the discussion of the results of these studies in a broader perspective, including their implications for practice, policy and research.

1.5 Data sources

Two data sources have been used to answer the research questions addressed in this thesis: data from the Global Influenza B Study and the WHO FluNet database.

1.5.1 The Global Influenza B Study

The Global Influenza B Study was launched in 2012 with the aim to collect information on the epidemiology of influenza B since 2000 and to produce the evidence needed to help support future influenza prevention policies globally. The study database was established by contacting representatives of surveillance systems in over fifty countries in the Northern and Southern hemispheres and the inter-tropical belt. Overall, participants from thirty countries (accounting for over one third of world's population) agreed to join the study: these were asked to make data available originating from their national influenza surveillance system during recent years (ideally, from 2000 onwards). The data requested from each country included the weekly influenza-like illness/acute respiratory infection consultation rates; the weekly number of respiratory specimens tested for influenza viruses; and the weekly number of influenza-positive specimens by age of the patient and virus type, subtype, and lineage. In addition, information was collected on characteristics and features of the influenza surveillance system from which the provided data originated. The rationale and methodology of the Global Influenza B Study are described in detail in chapter 2. The database of the Global Influenza B Study has been used for the studies reported in chapters 2 to 5 of this thesis.

1.5.2 The WHO FluNet database

We resorted to the WHO FluNet database, a publicly available, web-based database operated by the WHO [46-47], to conduct the analyses presented in chapters 6 and 7. National Influenza Centres (NICs) and other influenza reference laboratories that participate in the Global Influenza Surveillance and Response System have been entering influenza surveillance data into the FluNet database since 1995. The FluNet database contains virological surveillance data (weekly number of laboratory-confirmed influenza cases by type, subtype and lineage) from the majority of countries in the WHO European region, which was a necessary condition so that the research questions of chapters 6 and 7 could be answered in an appropriate and valid way.

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